Remarks

Receipt is acknowledged of the Office Action of June 19, 2002. Reconsideration of the application and a two month extension of the time provided for a response are requested. A check for $920 in payment of the three month extension fee is enclosed. Should any further fees be necessary, the Commissioner is hereby authorized to charge Deposit Account 50-1604 for all amounts required.

In the Office Action, the Examiner rejected Claims 1-19 under 35 U.S.C. §112 for use of the language "capable of emitting". In response, the claims have been amended to address the Examiner's rejection. The amended claims merely recite the presence of a label, the term being known to one of ordinary skill in the art. No narrowing of the claims is intended. In addition, various other change have been made to the claims, including modification of the term "containing" to "comprising" so as to use open language that slightly broadens the claims' scope, and modification of the term "the" to "said" in various locations as a more consistent means of reciting antecedent basis. None of the changes to Claims 1-19 are meant to narrow the claims' scope.

Claim 1 was also rejected under §112 for use of the term "plurality of features", with clarification being requested by the Examiner. As used in the claims and as defined in the specification, the term "plurality of features" refers to the fact that multiple spots are provided on the microarray (the spots each being provided with nucleic acid). *See e.g.,* specification at page 2 line 7.

In the Office Action, the Examiner also rejected Claims 1, 7-8, 10-11, 13 and 18 under 35 U.S.C. §102(b) based on the Nilsen reference (U.S. Patent No. 5,487,973) and Claims 2-6, 9, 12, 14-17 and 19 under 35 U.S.C. §103(a) based on the Nilsen reference in combination with Wang (U.S. Patent No. 6,004,755). Reconsideration of the rejections is respectfully requested.

As set forth in the application, the present invention is directed to an expedited method of assaying and detecting nucleic acid sequences. In accordance with a preferred embodiment of the

invention, a microarray is used for the nucleic acid analysis. A microarray is a substrate having a grid of tiny spots (also referred to herein as features), each spot having millions of copies of a short sequence of DNA or nucleotides. A computer keeps track of the specific sequence which is located at each spot or feature. The microarray therefore allows assay of extremely large numbers of different spots virtually simultaneously. In other words, the microarray allows one to very quickly conduct thousands of individual "test-tube" like experiments on a single substrate, providing enormous savings of time and increased efficiency.

Further in accordance with the invention, a capture reagent is used in conjunction with the microarray to assay nucleic acid in a desired sample. In the preferred embodiment, the capture reagent is a dendridic nucleic acid molecule ("a dendrimer"). A dendrimer is a highly branched molecule made up of a plurality of "arms" of nucleic acid. Preferably, the dendrimer has two types of arms: one arm is used to attach a specific targeting molecule, and the other arm is used to attach a label. A single dendrimer can be provided with hundreds of each arm, providing a high degree of both targeting efficiency and labelling efficiency. In a further preferred embodiment of the invention, the target molecule is a cDNA, which is used to hybridize to nucleic acids in the features of the microarray.

In the Nilsen reference, a method is discussed for preparation of dendrimers and for conducting research therewith. Upon review of the document, however, counsel has been unable to find any reference in Nilsen which teaches or suggests a method for use of microarrays in conjunction with dendridic nucleic acids. Nor has counsel been able to find any teaching or suggestion of a method for preparation of cDNA reagents or hybridization of such cDNA reagents to one of the dendrimer's arms. To anticipate a claim under §102(b), however, the reference must teach every element of the claim. *See,* MPEP §2131 (8th Ed., page 2100-69). Since Nilsen does not teach or suggest the user of microarrays or cDNA reagents, it submitted that Nilsen is not prior art to the present invention under §102(b), and

it requested that the rejection over the Nilsen reference be withdrawn.

In the Office Action, the Examiner further rejected the claims of the invention under 35 U.S.C. §103 based on Nilsen in conjunction with Wang reference. Wang, however, does not teach the assay of cDNA on a microarray using dendritic nucleic acid reagents. Nor is there any teaching or suggestion in Nilsen or Wang to combine the references.

Moreover, Claims 1 and 18 of the present invention are directed to a new "one-step" hybridization which is not disclosed or suggested in either Wang or Nilsen. In the assay method previously used by the present inventor (the "two step process"), it was necessary to first incubate the cDNA reagent to the microarray overnight, to hybridize that reagent to any complementary spots on the microarray. After this overnight incubation, the labelled dendritic reagent was then subsequently applied to that microarray and also incubated overnight, to hybridize the labelled dendritic reagent to any cDNA hybridized to the array, thereby generating a hybridization pattern. This process of first hybridizing the cDNA to the array, and then subsequently hybridizing the labelled probe reagent to the cDNA on that array, was very time consuming, requiring two overnight hybridizations.

In contrast, further to the present invention, a method has been developed in which the prior process has been replaced by a new "one-step" technique. In one embodiment of this one-step technique, pre-hybridization is conducted of the cDNA and the dendrimer together before application of the cDNA to the microarray, eliminating one full step of overnight hybridization. (*See e.g.*, Claim 18, which recites this prehybridization embodiment). In an alternate embodiment, the cDNA and dendrimer are concurrently both applied to the microarray, for simultaneous hybridization of the cDNA to both the microarray and the dendrimer. (*See e.g.*, Claim 1, which recites this embodiment – i.e the mixing step of Claim 1 can be conducted prior to application of the first and second components to the microarray, or the mixing can occur on the microarray). This embodiment also eliminates an entire

overnight hybridization. Accordingly, the time needed for the assay procedure of the present invention is considerably shortened over prior methods. This is an important advantage, significantly reducing the time needed to obtain experimental results.

This "one-step" method is a significant advance over the cited art and is claimed in Claims 1 and 18. Claim 1 recites the embodiment wherein a mixture containing both the cDNA and the dendrimer is applied to the microarray, allowing hybridization of the dendrimer to the cDNA and concurrent hybridization of the cDNA to the spots of the array. Claim 18 recites the embodiment wherein a mixture is first prepared of both the cDNA and the labelled dendrimer, to form a complex of the cDNA with labelled dendrimer, with that labelled pre-hybridized cDNA-dendrimer complex then being applied to the microarray.

The cited art does not teach these claimed one-step processes, individually or when considered in combination. Wang generally includes some discussion of labels that provide a detectable signal through capture moieties that specifically bind to complementary binding pair members (*See,* Col. 4 lines 25 - 41), and subsequently discusses those labels in connection with a two-step process. Specifically, when considering those labels, Wang discloses that one contacts the array with the target nucleic acid and then, once hybridization of the nucleic acid target with the array is completed, one then subsequently contacts the array with the other member of the signal producing system that is being employed. *See,* Col. 7 lines 8-11. This is a "two-step" process, in direct contrast to the "one-step" process of the present invention.

Present Claims 1 and 18 are also not obvious over a combination of the cited references due to the considerably different methods which are being employed. In addition to reciting one-step methods, the present claims also recite the use of capture sequences. This is also not taught or suggested in the art of record.

In the method of the Wang reference, a method is discussed involving reverse transcription of mRNA message into cDNA, and subsequent application of the cDNA to a microarray. In the method disclosed in the Nilsen reference, the dendrimer probes are created for analysis of a particular target nucleic acid which is to be studied. This is accomplished by synthesizing an arm for the dendrimer probe which will have a sequence complementary to a particular sequence on the target nucleic acid to be studied. *See e.g.,* Col. 17 lines 30-54 and Col. 19 lines 45-60.

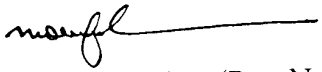
If the two references were combined, based on their combined disclosures a dendrimer probe would have to be synthesized for each of the cDNA sequences to be studied. When dealing with the case of a microarray assay, this would require the creation of at least 30,000 different dendrimers, one for each cDNA copy of the different mRNA messages. This method would be extremely burdensome and impractical. Accordingly, it would not at all be obvious to combine the cited references.

The present invention avoids this problem by providing or using a common capture sequence on the different cDNAs for hybridization of those various cDNAs to a complementary sequence provided on the dendrimer arm. Accordingly, a single complementary sequence can be used to universally allow a single type of dendrimer to hybridize to any and all of the cDNAs in the sample, without the need to create multiple dendrimers. This aspect of the invention is recited in Claims 1 and 18. Neither Nilsen nor Wang, nor their combination teach or suggest the use of capture sequences to link a single type of dendrimer to all of the cDNAs reverse transcribed from a sample of mRNA.

In view of the above, reconsideration of the application is respectfully requested.

Dated: December 19, 2002

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of:	Robert Getts	**Patent Application**
Serial No.:	09/802,162	
Art Unit:	1637	
Filing Date:	3/08/2001	
For:	Methods for Assay and Detection on a Microarray	
Attorney Docket No.:	4081.005	

Commissioner for Patents
Washington, D.C. 20231

Marked-Up Amended Claims

For the Examiner's reference and pursuant to 37 C.F.R. 1.121, a marked-up version of the amended claims is provided as follows:

1. (Once Amended) A method for detection and assay on a microarray, said method comprising the steps of:

1) contacting a microarray having thereon a plurality of features each [containing] comprising a first particular first nucleotide sequence with a mixture [containing] comprising:

a) a first component comprising a cDNA reagent obtained from mRNA of a target sample, said cDNA having a capture sequence; and

b) a second component comprising a dendrimer having at least one first arm [containing] comprising a label [capable of emitting a detectable signal] and at least one second arm having a second nucleotide sequence complementary to [the] said capture

sequence;

2) mixing [the] said first and second components at a temperature and for a time sufficient to enable [the] said first component to bind to [the] said second component; and

3) incubating this mixture with said microarray to enable the first nucleotide sequence to bind to [the] said first component, wherein such binding results in the [feature emitting the detectable signal] generation of a hybridization pattern on the microarray.

18. (Once Amended) A method for detection and assay on a microarray, said method comprising the steps of:

1) incubating a mixture including:

i) a first component comprising a cDNA reagent obtained from mRNA of a target sample, said cDNA having a capture sequence; and

ii) a second component comprising a dendrimer having at least one first arm [containing] comprising a label [capable of emitting a detectable signal] and at least one second arm having a second nucleotide sequence complementary to [the] said capture sequence,

at a first temperature and for a time sufficient to induce [the] said first component to bind to [the] said second component [and] to form a prehybridized cDNA-dendrimer complex;

2) contacting a microarray having thereon a plurality of features each [containing] comprising a particular first nucleotide sequence with said mixture; and

3) incubating [the] said microarray and [the] said prehybridized cDNA-dendrimer complex at a second temperature and for a time sufficient to induce [the] said

prehybridized cDNA-dendrimer complex to bind to [the] said first nucleotide sequence, wherein such binding results in the [feature emitting the detectable signal whereby] generation of a hybridization pattern [is generated] on [the] said microarray.

Dated: December 19, 2002

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